Remarks/Arguments

The foregoing amendments are of formal nature, and do not add new matter. Their entry is respectfully requested.

Claims 39-51 are pending in this application. Although the Examiner has withdrawn prior rejections to the claims under 35 U.S.C. §112, second paragraph, all claims remain rejected under 35 U.S.C. §101 utility requirement; the 35 U.S.C. §112, first paragraph "how to use" requirement; and the 35 U.S.C. §102 and §103. In addition, the Examiner has raised a new objection/ rejection to Claim 39-43, 50 and 51.

Applicants respectfully traverse the present rejections.

Specification

Applicants have amended the specification to remove the hyperlinks embedded in the specification, as indicated by the Examiner.

Formal Matters

Applicants thank the Examiner for acknowledging the deposit of the organism, ATCC 209250.

Priority

Applicants rely on the gene amplification assay (Example 92) to establish patentable utility for the claimed polypeptide, PRO232. These results were first disclosed in U.S. Provisional Application 60/059121, filed September 17, 1997 and hence, the present application is entitled to this effective filing date.

As will be apparent from our discussions below, the Declaration by Dr. Avi Ashkenazi, filed under 37 C.F.R. §1.132, in conjunction with the results of the gene amplification assay in the specification, provide specific and substantial asserted utility for the claimed polypeptides in this invention.

Claim Rejections – 35 U.S.C. §101/ 112, First Paragraph

Claims 39-51 are rejected under 35 U.S.C. §101/112, first paragraph, for not being supported by either a specific or substantial utility for PRO232. The Examiner asserts on page 5, line 1-3 that, the data regarding gene amplification may be applicable to nucleic acid molecules but does not correlate with increased amounts of protein. Citing Pennica *et al.,* and Haynes *et al.,* the Examiner adds "the data do not

support the implicit assertion that the PRO232 polypeptide can be used as a cancer diagnostic. Additionally, there is no evidence of record that the encoded protein plays any role in tumor formation and/or growth."

Applicants respectfully disagree.

Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. §101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

A prima facie case of lack of utility has not been established

The Examiner bases the conclusion of lack of utility on a quote from Pennica *et al.* which says, "WISP-2 DNA genomic DNA was amplified in colon tumors but its mRNA expression was significantly reduced in the majority of the tumors" and also, based on a quote from Haynes *et al.* "For **some** genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold." From this, the Examiner correctly concludes that increased copy number does not *necessarily* result in

increased protein expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation between gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides or the 80 proteins with relatively homogenous half-life and expression levels is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level.

Even if a prima facie case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence

Even if one assumes arguendo that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility.

Enclosed is a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the present application. As Dr Ashkenazi explains,

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Accordingly, the PRO 232 polypeptide has a substantial specific utility, and the present rejections under 35 U.S.C. §101/112, first paragraph, should be withdrawn.

Claim Rejections – 35 U.S.C. §112, First Paragraph

Claims 39-51 are rejected under 35 U.S.C. §112, first paragraph, for failing to comply with the enablement requirement. The Examiner asserts that claims do not recite a functional limitation and encompass an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use.

In view of the cancellations of Claims 39-43, the Ashkenazi declaration and the discussions above regarding the utility of the polypeptides, Applicants submit that Claims 44-47 and 49-51 satisfy the enablement requirement because one skilled in the art would know how to make and use the claimed polypeptides for diagnosis of cancer. Hence, this rejection should be withdrawn.

Claim Rejections – 35 U.S.C. §112, First Paragraph

Claims 39-44 and 50-51 are rejected under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement.

Again, in view of the cancellation of Claims 39-43 and amendment of Claims 44 and 50, Applicants submit that one of skill in the art would know that Applicants had possession of the claimed invention. Hence, this rejection should be withdrawn.

Claim Rejections – 35 U.S.C. §112, Second Paragraph

Pending claims are rejected under 35 U.S.C. §112, second paragraph, for being indefinite. The Examiner asserts that the recitation that the claimed protein comprises an "extracellular domain" and that "the extracellular domain.... lacking its associated signal sequence" was indefinite since PRO232 was a soluble protein.

Applicants have canceled these recitations in Claim 44 and instead, recite "soluble" protein. Hence, these claims are now definite.

Claim Rejections – 35 U.S.C. §102(b)

Claims 39-42, 50, 51 were rejected under are rejected under 35 U.S.C. §102 (b) as being allegedly anticipated by Rosenthal (dated 28 October, 1999) which discloses a nucleic acid molecule with 95-98% identity to SEQ ID NO: 18 of the present application.

The rejection is moot with respect to Claims 39-43 in view of their cancellation. As discussed above, the pending claims are entitled to the effective filing date of

September 17, 1997. The effective date of the cited primary reference after the effective filing date of the present application. Hence, Rosenthal is not prior art under 102(b).

Hence Applicants request that this rejection be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-1618 P2C18**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: December 10, 2003

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